ORIGINAL RESEARCH

C_2HEST Score and Prediction of Incident Atrial Fibrillation in Poststroke Patients: A French Nationwide Study

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***Background*—**The C_2HEST score (coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age ≥75 years, 2 points]; systolic heart failure [2 points]; thyroid disease [hyperthyroidism, 1 point]) was initially proposed for predicting incident atrial fibrillation (AF) in the general population. Its performance in poststroke patients remains to be established, especially because patients at high risk for incident AF should be targeted for more comprehensive screening. This study aimed to evaluate this newly established incident AF prediction risk score in a post–ischemic stroke population.

***Methods and Results*—**Validation was based on a hospital-based nationwide cohort with 240 459 French post–ischemic stroke patients. Kaplan–Meier curves for incident rate of AF depict differences between varying risk categories. Discrimination of the C_2HEST score was evaluated using the C index, the net reclassification index, integrated discriminatory improvement, and decision curve analysis. During 7.9±11.5 months of follow-up, 14 095 patients developed incident AF. The incidence of AF increased from 23.5 per 1000 patient-years in patients with a C_2HEST score of 0 to 196.8 per 1000 patient-years in patients with a C_2HEST score ≥6. Kaplan–Meier curves showed a clear difference among different risk strata (log-rank P<0.0001). The C_2HEST score had good discrimination with a C index of 0.734 (95% CI, 0.732–0.736), which was better than the Framingham risk score and the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65 to 74 years, and female sex) (P<0.0001, respectively). The C_2HEST score was also superior to the Framingham risk score and the CHA_2DS_2-VASc score as shown by the net reclassification index, integrated discriminatory improvement (P<0.0001, respectively) and decision curve analysis.

***Conclusions*—**The C_2HEST score performed well in discriminating the individual risk of developing incident AF in a white European population hospitalized with previous ischemic stroke. This simple score may potentially be used as a risk stratification tool for decision making in relation to a screening strategy for AF in post–ischemic stroke patients. **(*J Am Heart Assoc*. 2019;8:e012546. DOI: 10.1161/JAHA.119.012546.)**

Key Words: atrial fibrillation • cohort study • ischemic stroke • risk score

Atrial fibrillation (AF) is the most common sustained arrhythmia, with increasing prevalence and incidence worldwide.[1–4] Many AF patients are asymptomatic or have nonspecific symptoms, and a large proportion remain undiagnosed.[5] These asymptomatic patients may at higher risks of thromboembolic events and mortality compared with patient

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Received March 6, 2019; accepted May 1, 2019.

Clinical Perspective

What Is New?

- The C_2HEST score, a simple clinical risk stratification model, has been proposed to predict incident atrial fibrillation among Asian patients.
- In the nationwide analysis of 240 459 patients with previous ischemic stroke in France, we found that the C_2HEST score performed well in discriminating the individual risk of developing incident atrial fibrillation.

What Are the Clinical Implications?

- The simple C_2HEST score has potential to be used as a risk stratification tool for decision making in relation to a screening strategy for atrial fibrillation in poststroke non-Asian patients.

who have symptoms.[6] Some would be identified with AF only after their presentation with a major complication, such as stroke or heart failure (HF).[7]

Individual risk evaluation for developing incident AF is important for the decision-making process of early primary prevention and detection of AF, which may associate with better outcomes.[8] A simple clinical risk-evaluation tool may facilitate effective and cost-effective prevention and screening strategies for incident AF. Such a tool may help identify patients at high risk for incident AF who can be targeted for more intensive screening programs and primary prevention strategies.

A simple clinical risk-stratification model, the C_2HEST score (coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age ≥75 years, 2 points]; systolic HF [2 points]; thyroid disease [hyperthyroidism, 1 point]) was recently proposed to predict incident AF among Asian patients.[9] This score was derived from a large cohort of 471 446 Chinese patients[10] and was validated in the Korean National Health Insurance Service Health Screening cohort with 514 764 Korean patients.[11] The risk of incident AF increased significantly with higher C_2HEST score.[9]

Current guidelines recommend that poststroke patients need AF screening.[12] However, diverse screening approaches may have different capabilities in detecting unrevealed AF; perhaps more aggressive screening methods should be used for patients who are more likely to develop incident AF,[13] enabling an effective and cost-effective screening strategy. The present study aimed to assess whether the newly established risk model, the C_2HEST score, could predict AF in patients with previous ischemic stroke and without known prior AF and whether it could stratify poststroke patients into different risk groups for incident AF.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. This longitudinal cohort study was based on a national hospitalization database in France covering hospital care across the entire population. In France, each hospital discharge, whether from a public or a private hospital, must be registered in the National Hospital Discharge Database (PMSI [Programme de Médicalisation des Systèmes d'Information]).[14] A standardized discharge summary is collected for every hospital stay in France and categorized into a single medical or surgical diagnosis-related group based on the diagnosis and procedures coded, inspired by the US Medicare system.[15] Since 2001, a unique patient identification number has made it possible to link multiple hospital stays corresponding to a single patient without revealing his or her identity. Since 2004, each hospital's budget has been linked to the medical activity described in this specific program, which compiles discharge abstracts related to all admissions for inpatients in the 1546 French healthcare facilities. The *International Classification of Diseases, Tenth Revision (ICD-10)* has been used to code discharge diagnoses since 1996. The main outcome measure was the rate of incident AF.

Data for all patients admitted with ischemic stroke in France from January 2008 to December 2012 were collected from the PMSI using the annually updated versions of the *ICD-10* for the years 2008–2012. The reliability of PMSI data has already been assessed[16] and used previously to study patients with stroke and AF.[17,18]

The medical information contained in the database is anonymous and protected by professional confidentiality. Consequently, ethics review was not required. Patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care. This type of study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 1, 2015, and registered as a clinical audit. Procedures for data collection and management were approved by the Conseil National de l'Informatique et des Libertés, the independent national ethics committee protecting human rights in France, which ensures that all information is kept confidential and anonymous (authorization no. 1749007). The study included adults (aged ≥18 years) with a diagnosis of acute ischemic stroke (code I63 and its subsections using *ICD-10*) coded as the primary diagnosis (ie, the health problem that justified admission to hospital), the related diagnosis (ie, potential chronic disease or health state during hospital stay), or the significantly associated diagnosis (ie, comorbidity or associated complication) who were hospitalized between January 1, 2008, and December 31, 2012. We

performed an analysis restricted to the patients seen after 2009, meaning that all patients had at least 1 year in which previous events were recorded to establish history of previous AF and comorbidities. Patients with no diagnosis of AF were considered to have sinus rhythm. Of note, asymptomatic cerebrovascular diseases and sequelae of stroke have different codes (I65, I66, and I69 with subdivisions) to be distinguished from acute strokes and were not included in our analysis. We calculated the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65 to 74 years, and female sex) and C_2HEST scores, as described previously.[9,19] Because both hypo- and hyperthyroidism have been associated with AF,[20,21] we used a more general item of *thyroid disease* instead of *hyperthyroidism* when calculating the C_2HEST score. We also performed a sensitivity analysis with the C_2HEST score using hyperthyroidism only. We also calculated a modified Framingham risk score based on its initial description.[22]

Statistical Analysis

Qualitative variables were described using counts and percentages, and continuous quantitative variables were described as mean±SD or median (interquartile range). Comparisons were made using parametric or nonparametric tests, as appropriate: The Wilcoxon signed rank and Kruskal–Wallis tests were used for comparing values between 2 independent groups, and the χ^2 test was used to compare categorical data. The population of individuals seen with ischemic stroke without prior AF was analyzed by calculating incidence rates of new-onset AF and by multivariable Cox regression models. A proportional hazards model was used to identify independent characteristics associated with the occurrence of AF during follow-up. Receiver operating characteristic curves were constructed, and Harrell C indexes (ie, area under the curve) were calculated as a measure of model performance and compared using the DeLong test. Integrated discriminatory improvement and net reclassification improvement were calculated according to the methods described by Pencina et al[23] to assess the discrimination and reclassification performance of the scores. Clinical usefulness and net benefit of the C_2HEST score in comparison to the CHA_2DS_2-VASc score and the Framingham risk score were estimated using decision curve analysis.[24,25] In all analyses, $P<0.05$ was considered statistically significant. All analyses were performed using JMP 9.0.1 (SAS Institute) and STATA v12.0 (StataCorp).

Results

A total of 240 459 patients were included in the analysis. During follow-up, 14 095 patients developed incident AF, which give us 158 302 person-years of experience (mean follow-up of 7.9±11.5 months). Baseline characteristics are presented in Table 1. Patients with AF were older than those without AF ($P<0.0001$), and more were female ($P<0.0001$). The prevalence of each comorbidity was higher in AF patients, including hypertension, diabetes mellitus, coronary arterial disease, valve disease, hyperlipidemia, vascular disease, chronic obstructive pulmonary disease, renal dysfunction, thyroid disease, and HF ($P<0.0001$, respectively). Patients who developed AF had higher CHA_2DS_2-VASc scores at baseline than those who did not develop AF ($P<0.0001$).

Results of the Cox multivariable regression analysis for incident AF are shown in Table 2. On multivariable analysis, HF, age ≥75 years, coronary arterial disease, valve disease, chronic obstructive pulmonary disease, hypertension, and renal dysfunction were shown to be independently related to the development of incident AF. HF and age ≥75 years were the most potent risk factors for incident AF, with hazard ratios (HRs) >2.0.

The incident rate of AF increased significantly with higher C_2HEST scores (Figure 1). The HRs for incident AF increased with higher score and risk group (Figure 2). When divided into 3 groups by baseline C_2HEST score, annual incidence rates were 3.19% in the low-risk group (0 or 1 point), 7.15% in the medium-risk group (2 or 3 points), and 14.64% in the high-risk group (≥4 points). The Kaplan–Meier curves for the 3 risk categories showed a graded increased risk for incident AF across risk groups (log-rank $P<0.0001$; Figure 3).

The C_2HEST score showed good discriminative ability with a C index of 0.734 (95% CI, 0.732–0.736), which was significantly better than the CHA_2DS_2-VASc score (0.703; 95% CI, 0.701–0.704; $P<0.0001$) and the Framingham risk score (0.720; 95% CI, 0.718–0.722; $P<0.0001$; Figure 4A). These results with the C_2HEST score using an item of thyroid disease including hypo- or hyperthyroidism were marginally better than the sensitivity analysis with the score calculated using hyperthyroidism only (C index: 0.716; 95% CI, 0.714–0.718). The discriminative ability of the C_2HEST score was also assessed with regard to sex, showing satisfactory results in both men (C index: 0.741; 95% CI, 0.735–0.747) and women (C index: 0.724; 95% CI, 0.718–0.729). Among elderly patients (aged ≥75 years), the C_2HEST score could also discriminate for different risk strata in relation to incident AF (C index: 0.694; 95% CI, 0.689–0.700; for patients aged <75 years: C index: 0.735; 95% CI, 0.728–0.743).

The C_2HEST score had positive net reclassification improvement and integrated discriminatory improvement compared with the CHA_2DS_2-VASc score (23.6% [$P<0.0001$] and 31.0% [$P<0.0001$], respectively) and the Framingham risk score (6.7% [$P<0.0001$] and 12.0% [$P<0.0001$], respectively). Using decision curve analysis, the C_2HEST score showed better clinical usefulness compared with the CHA_2DS_2-VASc and Framingham risk scores (Figure 4B).

Table 1. Baseline Characteristics of 240 459 Patients Included in the Study

Characteristics	Patients Without AF (n=226 364)	Patients With Incident AF (n=14 095)	*P* Value
Age, y, mean±SD	70.8±15.7	77.6±10.6	<0.0001
Male sex, n (%)	119 098 (53.0)	7013 (50.0)	<0.0001
Medical history, n (%)			
Hypertension	141 045 (62.3)	11 745 (83.3)	<0.0001
Diabetes mellitus	50 977 (22.5)	4083 (29.0)	<0.0001
Coronary arterial disease	39 652 (17.5)	4969 (35.3)	<0.0001
Valve disease	15 121 (6.7)	2780 (19.7)	<0.0001
Hyperlipidemia	69 428 (30.7)	5793 (41.1)	<0.0001
Vascular disease	70 636 (31.2)	6907 (49.0)	<0.0001
COPD	35 320 (15.6)	3661 (26.0)	<0.0001
Renal dysfunction	38 618 (17.1)	5393 (38.3)	<0.0001
Hyperthyroidism	3355 (1.5)	646 (4.6)	<0.0001
Thyroid disease	19 720 (8.7)	2525 (17.9)	<0.0001
HF	33 162 (14.7)	6261 (44.4)	<0.0001
CHA_2DS_2-VASc score, median (IQR)	5 (2)	6 (2)	<0.0001

Thyroid disease comprises hypo- and hyperthyroidism. CHA_2DS_2-VASc score is composed of congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65 to 74 years, and female sex. AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; IQR, interquartile range.

Discussion

This study is the first to externally validate the newly established C_2HEST score, a simple risk prediction model for incident AF, in a European cohort by using a nationwide (French) hospital-based white European population admitted with ischemic stroke. We found that the C_2HEST score performed well in discriminating the individual risk of developing incident AF in a white European population hospitalized with previous stroke. Given that poststroke patients at high risk incident AF should be targeted for more comprehensive screening, this simple score has the potential to be used as a risk-stratification tool for decision making in relation to a screening strategy for AF in poststroke patients.

The predictive performance of this risk score was statistically better than that of the CHA_2DS_2-VASc and Framingham risk scores, which have previously been shown to be useful for AF prediction.[22,26,27] As demonstrated by integrated discriminatory improvement and net reclassification improvement analyses, compared with CHA_2DS_2-VASc, 23.6% more of the studied population was correctly classified into the right risk group[28] and 31.0% more model sensitivity (with no loss of specificity) was obtained by the C_2HEST score.[29] Compared with the Framingham score, 6.7% of population was correctly reclassified and model sensitivity was increased by 12.0% with the C_2HEST score.

The independent risk factors in this newly established C_2HEST score were most common comorbidities among community and hospital-based populations. The definitions of these risk factors are relatively clear and support accessible and easy evaluation of patients' risk of developing incident AF.

On multivariable analysis, we found multiple independent risk factors for incident AF in our cohort, including coronary arterial disease, chronic obstructive pulmonary disease, hypertension, age ≥75 years, HF, and thyroid disease, all of which are constituents of the C_2HEST score. HF and age ≥75 years had higher HRs (>2), which were also considered major risk factors for incident AF in the C_2HEST score.[9] Nevertheless, some differences exist in our study compared with the original Asian cohort describing the C_2HEST score.[9] Because both hypo- and hyperthyroidism have been associated with AF,[20,21] we used a more general item of *thyroid disease* instead of *hyperthyroidism* when calculating the C_2HEST score, and this change showed slightly better predictive ability. We found that renal dysfunction was a risk factor in the present study but not an independent risk factor in Asian cohorts.[9] This result may be because of the different risk factor profiles among the different populations. In the European population, renal dysfunction may be a stronger risk factor for incident AF than in Asian patients.[30] For example, 2 studies from European populations reported renal impairment as an independent risk factor for incident AF, with HRs between 2.5 to 2.6.[31,32] In contrast, a report on a large cohort of 500 000 Asian patients found that renal dysfunction was not an independent risk factor (HR: 1.58; 95% CI, 0.78–3.20).[10] In another cohort from Taiwan (n=15 947), renal dysfunction showed an association with incident AF but with a relatively lower HR (1.46; 95% CI, 1.31–1.61)[33] compared with that reported in European populations. In this Taiwanese cohort, hemodialysis was analyzed as "renal dysfunction" but is a substantially more severe stage of this disease.[33]

We found the C_2HEST score performed well in discriminating individual risk of incident AF, and this ability was consistent in both sexes and in different age strata. When divided into different point ranges, incidence of AF increased with increasing C_2HEST scores. In addition, incidence of AF increased significantly with higher risk categorization, with an incident rate of 146.4 per 1000 person-years in the high-risk group (score ≥4). The C index for this score was also good in our white European cohort, consistent with the original derivation study from Asia.[9]

Several previously proposed risk models for predicting incident AF were derived from Western populations, including the Framingham risk score (Framingham Heart Survey),[22] the

Table 2. HRs of Risk Factors for Incident AF

	Univariate Analysis			Multivariable Analysis		
Risk Factors	HR	95% CI	*P* Value	HR	95% CI	*P* Value
HF	2.99	2.89–3.09	<0.0001	2.21	2.13–2.30	<0.0001
Age ≥75 y	2.54	2.45–2.63	<0.0001	2.11	2.04–2.19	<0.0001
Coronary arterial disease	1.70	1.64–1.76	<0.0001	1.09	1.05–1.13	<0.0001
Valve disease	2.26	2.18–2.36	<0.0001	1.42	1.36–1.48	<0.0001
Thyroid disease	1.71	1.64–1.79	<0.0001	1.36	1.31–1.43	<0.0001
COPD	1.42	1.36–1.47	<0.0001	1.18	1.14–1.22	<0.0001
Hypertension	1.90	1.81–1.98	<0.0001	1.34	1.27–1.40	<0.0001
Renal dysfunction	2.02	1.96–2.09	<0.0001	1.21	1.17–1.26	<0.0001
Hyperlipidemia	1.06	1.03–1.10	0.0005	0.87	0.84–0.90	<0.0001
Male sex	0.83	0.80–0.86	<0.0001	0.99	0.95–1.02	0.38
Diabetes mellitus	1.07	1.04–1.11	<0.0001	0.95	0.91–0.98	0.002
Vascular disease	1.42	1.37–1.46	<0.0001	0.93	0.90–0.97	<0.0001

Thyroid disease comprises hypo- and hyperthyroidism. CHA_2DS_2-VASc score is composed of congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65 to 74 years, and female sex. AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio.

ARIC (Atherosclerosis Risk in Communities) score,[34] the CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation) score,[35] and the STAF (Score for the Targeting of Atrial Fibrillation) score.[36] These risk scores had good discrimination for incident AF in their original studies; however, they require many instrumental and laboratory variables that might not be easily accessed in everyday practice. Furthermore, such complexity limits their daily application for operationalizing risk assessment in the real world, although they had good C indexes in the original studies.[37] Compared with the Framingham risk score (slightly modified), the C_2HEST score showed superiority for AF prediction in this poststroke patient population.

The $CHADS_2$, CHA_2DS_2-VASc, and HATCH (hypertension, age ≥75 years, transient ischemic attack or stroke [2 points], chronic obstructive pulmonary disease and HF [2 points]) scores also showed predictive capacity for incident AF in previous studies.[26,38] However, these scores were not derived for this purpose. Some components of these scores may not be risk factors for incident AF, such as female sex in the CHA_2DS_2-VASc score. In addition, stroke or transient ischemic attack does not increase an individual's risk of developing AF but may be an indicator of undiagnosed AF. Nevertheless, we previously compared the performance of these scores in predicting incident AF and demonstrated the better discriminative ability of the new C_2HEST score.[9]

In the present study, all patients had a history of ischemic stroke and thus should be candidates for screening of silent AF.[12,39] In the 2016 AF guidelines from the European Society of Cardiology, screening for AF using short-term ECG recording followed by continuous ECG monitoring for at least 72 hours is recommended in patients with ischemic stroke (class I recommendation with level B evidence), and additional ECG monitoring by long-term noninvasive ECG monitors or implanted loop recorders may be considered to document silent AF (class IIa recommendation with level B evidence).[12] However, only a limited number of patients receive AF screening because of the uncertainty about cost-effectiveness and the lack of robust evidence justifying the utility of AF screening.[40]

In our study, we found that patients with a C_2HEST score ≥4 had extremely high risk of developing incident AF (14.6% per person-year), justifying the need for more intensive ECG monitoring for silent or asymptomatic AF.[39] The availability of simple risk stratification may lead to a more effective and cost-effective, selective, opportunistic screening approach,[41,42] targeting patients at high risk of incident AF and its sequelae and supporting better adherence to guideline recommendations for AF screening. For instance, patients with extremely high C_2HEST scores should receive more intensive heart-rate monitoring, such as 1 to 2 weeks of Holter monitoring or an implantable loop recorder.

In the STROKESTOP (Massive Screening for Untreated Atrial Fibrillation) study, screening for asymptomatic AF in 75- or 76-year-old individuals was found to be cost-effective.[43] With a simple risk-assessment model, it would be possible to increase efficiency by targeting a more intensive screening

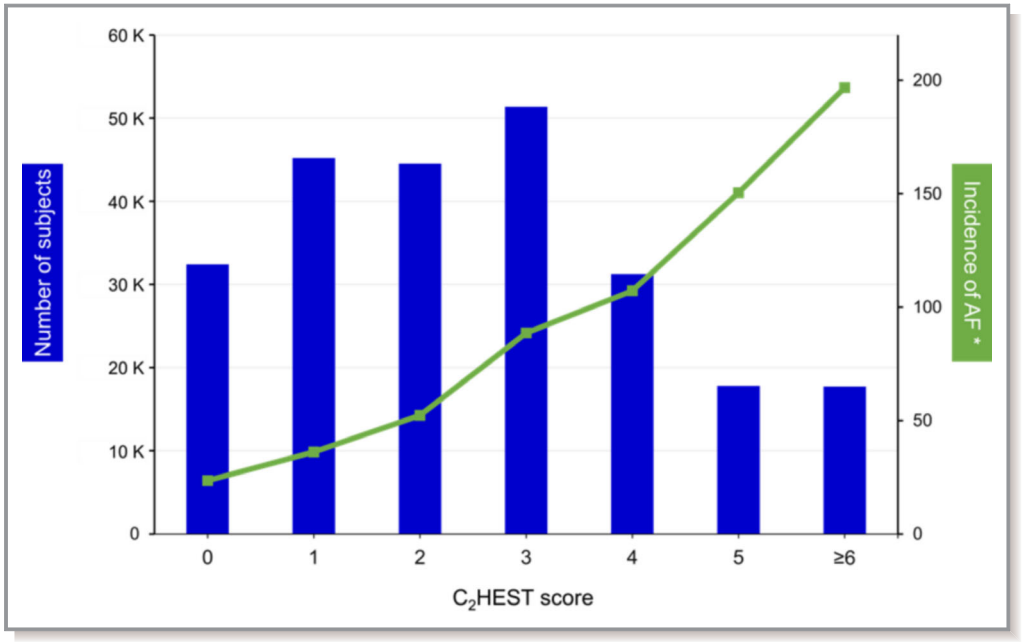

Figure 1. Prevalence of the C_2HEST scores and incident rate of atrial fibrillation (AF). *Per 1000 person-years.

approach among those at higher risk of developing incident AF.[44] In this study, we demonstrated that the C_2HEST score could further discriminate those at-risk elderly patients (aged ≥75 years) for AF. By initially calculating an individual C_2HEST score, conducting a more focused and cost-effective screening strategy may become more feasible.

Score	Subjects (No.)	AF Patients	Incidence of AF *	Hazard ratio	95% CI
0	32 404	309	23.5	1.00	--
1	45 181	968	36.1	1.56	1.38-1.78
2	44 531	1 485	52.3	2.29	2.03-2.59
3	51 379	2 831	88.6	3.92	3.49-4.42
4	31 264	2 640	107.2	4.84	4.31-5.46
5	17 816	2 341	150.5	6.99	6.22-7.89
≥ 6	17 731	3 521	196.8	9.66	8.61-10.9
Risk stratification					
Low (0-1)	77 585	1 277	31.9	1.00	--
Medium (2-3)	95 910	4 316	71.9	2.29	2.15-2.44
High (≥ 4)	66 811	8 502	146.4	4.97	4.69-5.27

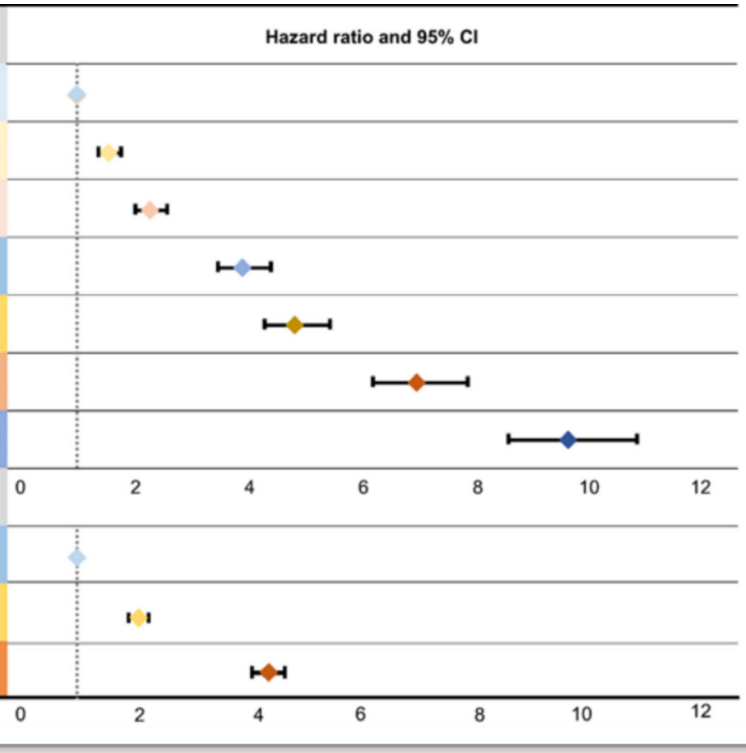

Figure 2. Annual incidence of atrial fibrillation (AF) by C_2HEST score. *Per 1000 person-years.

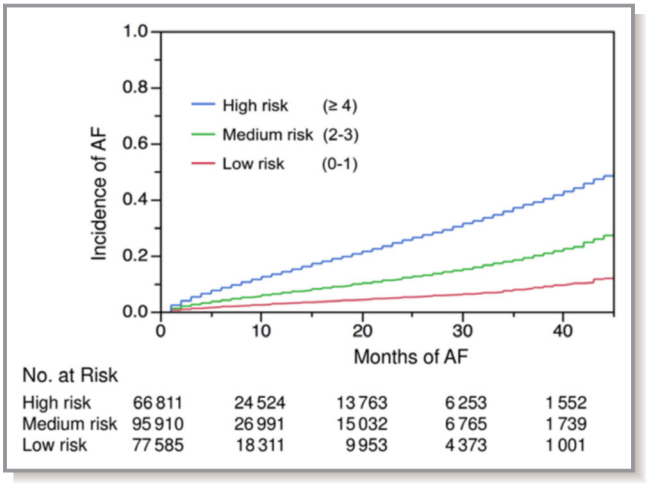

Figure 3. Kaplan–Meier curves of incidence of atrial fibrillation (AF) regarding different risk strata: low, 0 or 1 point; medium, 2 or 3 points; high, ≥4 points.

Strengths and Limitations

This study is the first external validation of the C_2HEST score in a large, nationwide, hospital-based, European population (French) with prior stroke history. We found that the C_2HEST score performed satisfactorily in evaluating the individual risk of developing incident AF after ischemic stroke, which may allow a targeted and tailored screening strategy in this population. Nevertheless, this study has some limitations. First, this hospital-based cohort study in France may not represent the general population. Incidental AF might be marginally underestimated if it were identified in only some outpatients during follow-up. Considering the way in which a history of AF might have been determined, a washout period of 1 year might be too short, and there is also a risk of underdiagnosis for prior AF in our population. We did not compare the performance of the C_2HEST score with other previously established scores, such as the ARIC, CHARGE-AF, or STAF scores, because some variables were unavailable in our data set to calculate those scores. For comparison with the Framingham risk score, we used a slightly modified model based on the original model, and this change may have introduced some difference from the original. Finally, some variables are known to influence the odds of detecting AF, such as chronic kidney disease, but are not included in the C_2HEST score. By including hyperthyroidism, the score may be biased for identification of circumstantial and transient causes of AF that may not be substantially relevant in terms of the decision to anticoagulate.

Conclusion

The C_2HEST score performed well in discriminating the individual risk of developing incident AF in a white European population hospitalized with previous stroke. This simple score has the potential to be used as a risk-stratification tool for decision making in relation to a screening strategy for AF in poststroke patients.

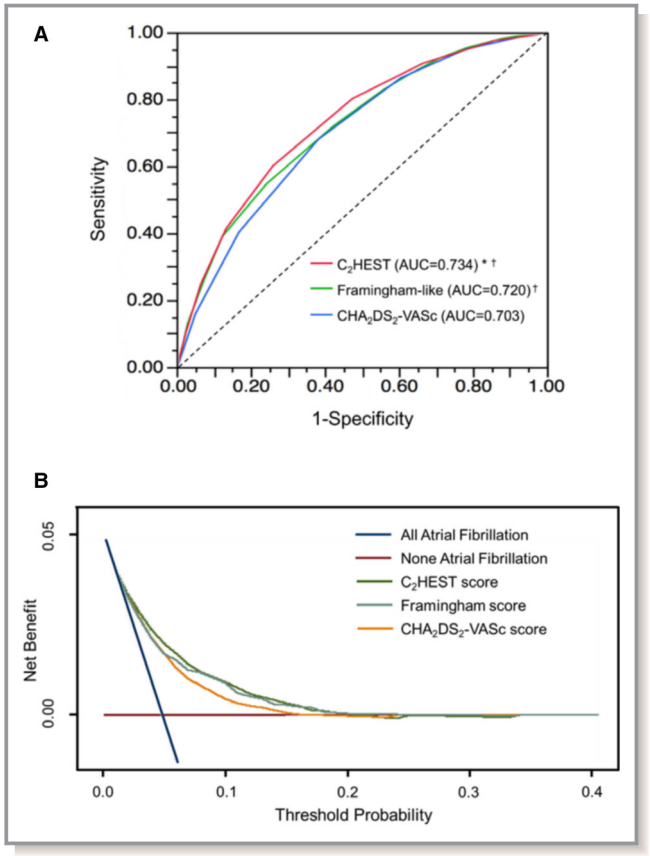

Figure 4. **A**, Receiver operating characteristic curves of incident atrial fibrillation developing during follow-up. *P<0.0001 vs Framingham risk score; †P<0.0001 vs CHA_2DS_2VASc score. **B**, Decision curve analyses for the C_2HEST, CHA_2DS_2-VASc, and Framingham risk scores. AUC indicates area under the curve.

Disclosures

Lip has been a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo; no fees are directly received personally. Fauchier has been a consultant or speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, and Novartis. Li has been a sponsored PhD trainee by the China Scholarship Council (201708110232). The remaining authors have no disclosures to report.

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